Mechanisms of action of general anesthetics
What Is Anesthesia?

A drug-induced reversible depression of the CNS resulting in the **loss of response** to and perception of all external stimuli.

**Broad definition:** all general anesthetics do not produce equal depression of all sensory modalities

**Not Broad:** not simply a deafferented state

**Anesthetic state (5c):**
- unconsciousness,
- amnesia,
- analgesia,
- immobility, &
- attenuation of autonomic responses to noxious stimulation
Goals of general Anesthesia:

- Prevent Pain
- Prevent **new memories**
- Relax muscles
- Suppress autonomic response
How inhaled anesthetics produce the anesthetic state?

- Their location of action within the CNS,
- The molecules with which they interact,
- The nature of this biologic interaction
Measurable and universal characteristics of all inhaled anesthetics include:

- Immobility measured by MAC (actions on the spinal cord)
- Amnesia (Supraspinal structures such as the amygdala, hippocampus, and cortex)
- Others (analgesia, skeletal muscle relaxation)
Central Nervous System Depression

- **Enhancing the function of inhibitory ion channels**
  - (Hyperpolarization by chloride influx through $\text{GABA}_A$ or glycine receptors or efflux of $\text{K}^+$ out of neurons through potassium ion channels)

- **Blocking the function of excitatory ion channels** [depolarization of the neuron]
  - (by preventing the passage of positive charges into the neuron i.e., passage of $\text{Na}^+$ through $\text{NMDA}$ receptors or sodium channels)

Affect release of neurotransmitters
**The Meyer–Overton Rule:** potency of gases as anesthetics was strongly correlated with their solubility in olive oil interpreted as lipids are likely to be the anesthetic target, [physical properties of cell membranes]

Anaesthetic potency (minimum alveolar concentration, MAC) correlated with lipid solubility. The more lipid soluble, the higher the potency.

The more soluble the inhaled anesthetic the higher the blood–gas partition coefficient.
Since a wide variety of structurally unrelated compounds obey the Meyer–Overton rule, it has been reasoned that all anesthetics are likely to **act at the same molecular site**.

**Unitary theory of anesthesia**

Anesthetics dissolve in the lipid bilayers of biologic membranes [asymmetric distribution] and produce anesthesia when they reach a critical concentration in the membrane.
The **Meyer–Overton rule** could also be explained by the direct interaction of anesthetics with hydrophobic sites on proteins:

Anesthetics can bind to **hydrophobic pockets** on proteins [(e.g., GABA_A and NMDA glutamate receptors, ion channels)] and that anesthetic–protein interactions can account for the Meyer–Overton rule
GABA\textsubscript{A} and NMDA glutamate receptors as targets for general anaesthetic action

**Central excitation**
- NMDA glutamate receptor
- \( \text{Ca}^{2+} \) (and \( \text{Na}^{+} \))
- Excitation

**Central inhibition**
- GABA\textsubscript{A} receptor
- \( \text{Cl}^{-} \)
- Hyperpolarization—Inhibition

**Awake**
- \( \uparrow \) Excitation
- \( \approx \) Inhibition

**Anaesthetized**
- \( \uparrow \) Inhibition
- \( \downarrow \) Excitation

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GABA, \( \gamma \)-aminobutyric acid; NMDA, N-methyl-D-aspartate
Propofol 3-Hyperpolarization
NMDAR is a glutamate receptor and ion channel protein found in nerve cells. NMDARs require the binding of 2 molecules of glutamate or aspartate and two of glycine. Memantine has been recognized to be an uncompetitive antagonist of the NMDA receptor.

Overactivation of the receptor, causing excessive influx of Ca\(^{2+}\) can lead to Excitotoxicity.
Structures of some common general anaesthetic agents along with their main targets

**Inhalational**
- Isoflurane
- Desflurane
- Sevoflurane

**Intravenous**
- Propofol
- Thiopental
- Etomidate
- Ketamine

**Major postsynaptic receptor**
How Do Anesthetics Interfere with the Electrophysiologic Function of the Nervous System?

By altering communication between neurons, generally occurring via synaptic transmission.
Anesthesia:
Connection between different parts of brain are lost

- **Network dysfunction**
Anesthesia consists of separable and independent components, each of which involves distinct, but possibly overlapping, mechanisms at different sites in the CNS.

The potencies of general anesthetics correlate with their solubility in oil, indicating the importance of interactions with predominantly hydrophobic targets.

General anesthetics act by binding directly to amphiphilic cavities in proteins.

The effects of inhaled anesthetics cannot be explained by a single molecular mechanism.

The immobilizing effect of inhaled anesthetics involves actions in the spinal cord, whereas sedation/hypnosis and amnesia involve supraspinal mechanisms that interact with endogenous memory, sleep, and consciousness pathways and networks.

Volatile inhaled anesthetics enhance inhibitory synaptic transmission postsynaptically by potentiating ligand-gated ion channels activated by GABA and glycine, extrasynaptically by enhancing GABA receptors, and presynaptically by enhancing basal GABA release.

Inhaled anesthetics suppress excitatory synaptic transmission presynaptically by reducing glutamate release (volatile anesthetics) and postsynaptically by inhibiting excitatory ionotropic receptors activated by glutamate.

There is as yet no comprehensive theory of anesthesia that describes the sequence of events leading from the interaction between an anesthetic molecule and its targets to the behavioral effects.